Ethics in Public Health Research

Anthrax Vaccine and Public Health Policy

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The Centers for Disease Control and Prevention has classified *Bacillus anthracis,* the causative organism of anthrax, as a category A potential bioterrorism agent.

There are critical shortcomings in the US anthrax vaccine program. Rather than depending on the private sector, the government must assume direct production of anthrax vaccine.

The development of a capacity capable of preemptive immunization of the public against anthrax should be considered. (*Am J Public Health.* 2007;97:1945–1951. doi:10.2105/AJPH.2006.102749)

THE CENTERS FOR DISEASE Control and Prevention (CDC) considers *Bacillus anthracis,* the causative organism of anthrax, to be a category A potential bioterrorism agent.[1] Anthrax vaccine adsorbed (AVA), which is made by BioPort (Lansing, Mich) under the name Biothrax, is the sole licensed anthrax vaccine in the United States and has been available since 1970. An inactivated vaccine derived from a cell-free filtrate, it is administered in a 6-dose series over 18 months and requires yearly boosters. Because of this logistical problem, the Institute of Medicine has called for development of a new anthrax vaccine.[2]

An analysis conducted by the Institute of Medicine found AVA to be safe,[2,3] but the validity of that report has been sharply criticized by Meryl Nass, a family physician and strong opponent of the vaccine,[4] and 450 military personnel have refused immunization.[5] Nass has claimed that the number of those adversely affected by the vaccine has been undercounted,[4] and 6 service members filed suit to halt the Department of Defense (DOD) program of mandatory vaccination for military personnel.[6] In October 2004, a US district judge issued an injunction halting the vaccination program on procedural grounds.[6] The program continued on a voluntary basis, with participation rates of 50%.[6] On December 19, 2005, The Food and Drug Administration (FDA) reaffirmed its earlier finding that the anthrax vaccine is safe and effective at preventing all forms of anthrax.[7] On October 16, 2006, DOD announced it would resume mandatory anthrax vaccinations, the procedural issues having been corrected.[6]

EFFICACY OF THE VACCINE

The clinical evidence for the efficacy of AVA comes from a 1950s industrial exposure study at 4 mills on a predecessor vaccine to AVA.[8] The FDA concedes that the number of cases of inhalational anthrax in that study (5 vs 21 cutaneous cases) "are too few in number to support a meaningful statistical conclusion."[7] It is from studies on primates that the FDA has concluded that the vaccine is effective in protecting humans against inhalational anthrax.[7]

AVA varies widely in efficacy among species. For instance, it provides no protection to hamsters.[9] In monkeys, however, studies have shown the vaccine to be protective against aerosolized spores at amounts 900 times the LD_{50} (the dose that would be expected to kill 50% of those exposed).[2]

Efficacy may be affected by genetic engineering. In Russia, Pomerantsev et al. reported that by taking the gene for cereolysin AB from *Bacillus cereus* and inserting it into *Bacillus anthracis* strains, they had created an anthrax strain that nullified the protective effect of the ST-1 anthrax vaccine in Syrian gold hamsters.[4,10]

ST-1 is a live spore vaccine made from a Russian strain of *Bacillus anthracis.*[11] As with the live spore vaccine licensed by the US Department of Agriculture for use in livestock, the spores germinate in the recipient to the vegetative form, which induces an antibody response to antigens, including protective antigen, an antigen required for the pathogenesis of anthrax. The antibody response is not directed solely against protective antigen, and it is unclear whether the reported circumvention of the Russian vaccine relates to AVA.

The Institute of Medicine dismissed this work, claiming it found 3 serious flaws in the study that made it "difficult to interpret the results."[2(p70)] The first of these was that the Syrian gold hamster was the test animal exposed to anthrax. Like the guinea pig, it may not be a good model because its response to vaccine may differ from that of primates.[2] In the guinea pig, for instance, vaccines directed solely against antigens such as protective antigen proved inadequate against many strains of *B anthracis.*[12] A recent study (subsequent to that of Pomerantsev et al.) demonstrated the same to be true for the Syrian gold hamster.[2]

The second claimed flaw was that Pomerantsev et al. did not report how many copies of the cereolysin genes were inserted and where they were located in the genome. The third was that antibodies to protective antigen were not measured. None of

these criticisms necessarily invalidate the substance of their report.

The Institute of Medicine believes that bioengineered *B anthracis* would probably not evade the American anthrax vaccine (AVA), because it is directed against a product of the bacteria—protective antigen—rather than the bacteria themselves.[2] The strategy of hostile bioengineering is to cloak the pathogen by altering its antigens or to genetically insert a toxin from pathogen A into infectious agent B.

The Institute of Medicine's reasoning is further based on the premise that protective antigen, which is necessary for the pathogenesis of anthrax in humans, cannot carry out the many processes that bring about this pathogenesis if even only a few of its subunits have been mutated. Thus, manipulation to alter its antigenicity would leave it ineffective, and by extension, the bacteria would be nontoxic.

In the remainder of this essay, we assume that the work of Pomerantsev et al. is either irrelevant to the US anthrax vaccine or is not reproducible, and that the Institute of Medicine is correct in assuming that the vaccine will remain effective. There are, however, real world problems related to anthrax vaccination that need to be addressed.

REALITY CHECK

BioPort (which was recently renamed Emergent BioSolutions) is the only licensed manufacturer of anthrax vaccine in the United States.[13] Privately held, BioPort was formed in 1998 to take over the assets of the state-owned Michigan Biological Products Institute (MBPI) in Lansing, Mich, the only facility in the United States that had been producing the vaccine.[14] BioPort paid $3.28 million in cash for MBPI, financing the rest of the $25 million cost with loans from the state of Michigan.[15] Eleven days after the sale was finalized, in September 1998, DOD awarded BioPort a $45 million contract to supply anthrax vaccine to the US armed forces.[16] The contract required the government to pay for up to 75% of the cost of the vaccine, even if the vaccine failed to be licensed for use.[13]

The Pentagon's intent was to begin a program that would eventually vaccinate all 2.4 million servicemen. The contract called for a unit price of $4.36 per injection for year 1 and $2.26 per injection for year 2 of the contract.[17] The cost approximated that which was charged when the facility was owned by the state of Michigan. Unfortunately, there were quality problems with the vaccine (many inherited from MBPI), and the facility failed inspection by the FDA, primarily because of improper sterilization procedures but also for unapproved methods of determining potency.[18,19]

BioPort's vaccine operations had been essentially suspended by the FDA in March 1997 (before the purchase), when the FDA issued a notice of intention to revoke its licensure unless deviations from FDA regulations were corrected.[20] The facility failed reinspections in February and October 1998.[20] In June 1999, BioPort notified the army that it was unable to continue operations unless it received additional funds, arguing that there were difficulties in bringing an undercapitalized former state health department laboratory up to current FDA standards for vaccine manufacturing. The Army Contract Adjustment Board, citing national security, granted "extraordinary contractual relief,"[17] increasing the contracted per-dose price to $10.46 and reducing the total amount of doses BioPort was required to provide.[17] The contract price was increased by $24 million, of which $18.7 million was given as an advance payment.[17]

The contract was made despite a report of the Pentagon's inspector general, whose auditors found that of the money that had already been advanced to the company, $1 million was spent on furnishing and renovating offices (including $23 000 for the chief executive officer's [CEO's] furniture), $1 million more was spent on other matters unrelated to anthrax production, and $1.28 million was spent on bonuses for senior management.[13,21,22]

In 2001, Congress and the Pentagon considered terminating the BioPort contract.[21] A report from DOD on possibly canceling the contract was due in September of that year.[22] It was noted that ending the contract would cripple Bioport.[23] On December 27, 2001, the company received FDA approval to resume licensed production.[24]

A major stockholder (at 13% ownership) is Admiral William Crowe, former chairman of the Joint Chiefs of Staff.[5] Crowe received his shares for agreeing to be on the board of directors of BioPort. According to his spokesperson, "He hasn't invested a penny in the venture."[14] From 2003 to September 2006, BioPort's revenues were $325 million, virtually all from sales of anthrax vaccine to DOD and the Department of Health and Human Services (HHS).[25]

The entrepreneur who created BioPort, Fuad El-Hibri, who is also its chairman and CEO, applied for US citizenship, on the advice of Crowe, to facilitate approval of BioPort's acquisition of MBPI.[21] El-Hibri, along with his wife and father, are controlling shareholders in BioPort through their ownership of Intervac LLC, which in turn is partially owned by I & F Holdings. I & F Holdings is a Netherlands Antilles holding company, owned by the same individuals and possibly other investors. Under Netherlands Antilles law, beneficial ownership of offshore companies need not be disclosed.[26]

There is little public information available about the controlling owners of BioPort. The CEO declined to return calls from ABC News reporters inquiring about Intervac and I & F Holdings.[14] Similarly, the company has declined to answer questions from an American newspaper.[21] The American public's only news sources on BioPort are a brief laudatory interview with El-Hibri in *USA Today*[27] and a short item in the *Washington Post*.[28]

MBPI is reported to have been purchased by BioPort without a national security

review[29]; it has been suggested that this was because of Admiral Crowe's presence on the board of directors.[30]

The current administration decided that it may not have been wise to rely on a single supplier. Financed through Project BioShield, a contract of $878 million was awarded to VaxGen in November 2004 for the production of 75 million doses of a recombinant bioengineered anthrax vaccine, an amount capable of inoculating 25 million people.[5]

VaxGen has never made a licensed vaccine and has a history of touting a failed AIDS vaccine.[5] VaxGen was delisted by the NASDAQ stock exchange in 2004 for failing to make timely financial reports.[5] Its anthrax vaccine decomposes, precluding stockpiling. The US Government terminated the contract in December 2006.[31]

In 2005, BioPort spent $595 000 on lobbying[32] (VaxGen spent $200 000 in the same year).[33] The firm of McKenna Long & Aldridge and the politically influential lobbyist John Hishta were brought in to secure an HHS contract for anthrax vaccine for the domestic stockpile.[21] In 2005, the HHS awarded BioPort a $122.7 million contract for 5 million additional doses of anthrax vaccine at a cost of $24.50 per dose.[34] The price per dose at year 2 of the original DOD contract was $2.26.

The order has since been doubled.[33] The president of BioPort has been quoted as saying that "foreign parties" were pleading to buy the vaccine at more than $100 per dose.[35]

BioPort was reorganized and renamed Emergent BioSolutions, with apparently identical ownership, and made an initial public offering in November 2006 to raise $92 million.[36] At the time of the offering, El-Hibri controlled 99.5% of Emergent BioSolutions' outstanding stock, a figure that dropped to 81.4% when the company went public.[37] In Securities and Exchange Commission documents, the company wrote that El-Hibri "will continue to have substantial control over us after the offering, including through his ability to control the election of the members of the board of directors, and could delay or prevent change of control."[37(p37)]

Currently on the board of directors are Louis W. Sullivan, who was HHS secretary from 1989 to 1993; Jerome M. Hauser, a former HHS official who oversaw public health emergency preparedness[36]; and Joseph Allbaugh, former director of the Federal Emergency Management Agency (FEMA).[38]

There has been an exodus of established, high-quality manufacturers from the American vaccine industry, the number declining from 26 in 1967 to 17 in 1980 to 5 in 2004.[39] The reasons for that exodus have been explored elsewhere.[40] The free market model does not work well when, for all practical purposes, there is but a single buyer (the government) that can set the price. Nor does it work well when there is but a single producer of a critical product—in such a market, the producer sets the terms.

The US pharmaceutical industry has had little financial incentive to develop new vaccines.[40] To fill the void, in the 1990s the Pentagon established the Joint Vaccine Acquisition Program. Under this program, DOD's own researchers create new vaccines, which are then handed to a private contractor who farms production out to yet another contractor. The system has been described by an independent panel in a DOD report as "a disaster."[41]

There is recent renewed involvement in vaccine manufacturing by large drug companies outside the United States.[42] The major US pharmaceutical companies, however, continue to show little interest in vaccine production for biodefense.[33]

PUBLIC POLICY CONSIDERATIONS

An independent panel for DOD proposed that the government develop and produce its own biodefense vaccines in a government-owned, contractor-operated production facility,[41] not only for the military but for the civilian population as well. The report, which was released 2 months before the September 11, 2001, attacks, calculated that it would cost $1.56 billion to build and operate such a plant for 25 years.[43] An antiterrorism panel created by Congress, the Gilmore Commission, came to an identical conclusion.[44] There is now, within this nation, a marked lack of infrastructure for vaccine production.[45]

Another option, criticized by some,[46] would be a government-owned, government-operated facility, perhaps modeled on the Manhattan Project. Expanding such a project beyond biodefense to encompass all vaccines has been proposed elsewhere.[47]

ANALYZING THE OPTIONS OF MASS PRODUCTION OF ANTHRAX VACCINE

There are 3 general positions on the mass production of anthrax vaccine: (1) vaccine is not necessary because the threat of an attack is remote, (2) vaccine is not necessary because antibiotics can be used instead, and (3) vaccine should be produced and stockpiled.

The Threat of an Anthrax Attack

A significant portion of the medical and scientific communities believes that the threat of biowarfare has been greatly exaggerated for political purposes, at the expense of current health problems.[48–50] One argument is that "there has been no example of effective use of anthrax as a weapon of indiscriminate mass destruction."[50(p1668)] Imperial Japan, however, in the period preceding and during World War II, sprayed anthrax spores on Chinese cities,[51] although there are no specific casualty figures. Japan also used other biological agents that killed approximately 10 000 people.[51]

Substate actors (terrorists organizations and cults) have also engaged in biological attacks—fortunately ineffective (the Aum

Shinrikyo cult) or at low levels (the Rajneeshes cult).[52]

The Aum Shinrikyo cult unwittingly failed to obtain a virulent strain for their anthrax attacks on Tokyo.[53] The perpetrator (or perpetrators) of the 2001 anthrax letters, however, had access to the virulent Ames strain.[54] That strain was widely distributed, present not only at the US vaccine production facility at BioPort but at 19 other laboratories in the United States and at sites overseas as well.[54,55]

Biological weapons have several advantages for the aggressor, not the least of which is the absence of a footprint. Even a release delivered through the US mail (the motive of which remains unknown) has proved untraceable. Those spores, identified in the press as being weaponized,[56] are now reported to have been a simple dry powder.[57,58] However, it has been noted that even a "crudely ground preparation" would have enough loose spores to be deadly.[57]

The limiting factor for governments and substate actors trying to spread anthrax spores is the technical hurdle of making dry powder. The difficulties and degree of expertise necessary to process anthrax spores into industrial quantities of dry agent are not explicitly described in generally available documents. In 1995, Iraq admitted to the United Nations Special Commission that it had "weaponized" anthrax.[59] Its weapons, however, were filled with anthrax slurry, which, because it is difficult to disperse as an effective aerosol, is of little use as a military weapon.[60]

Those who dispute the need for anthrax vaccine production point to Iraq's failure. The Soviet Union, on the other hand, despite signing the Biological Weapons Convention, in the 1970s embarked on an accelerated anthrax production and weaponization program.[61] Its facilities in the 1980s were reportedly capable of producing almost 5000 tons of highly virulent anthrax spores per year, although actual production was significantly lower.[62] The LD_{50} of the strain for mice was 5 spores, compared with the Ames strain's LD_{50} of 30 spores.[62]

If the supposition that the making of dry spores will remain an insurmountable obstacle for small states and substate actors should prove to be incorrect, the consequences could be dire. Animal studies suggest that the LD_{50} for humans is between 2500 and 55 000 inhaled anthrax spores.[59] However, studies on cynomolgus monkeys suggest that the LD_1 (the dose lethal to 1% of those exposed) for fine particles of anthrax spores may be as low as 1 to 3 spores.[63] The belief that so few spores could be lethal may be supported by a fatal case of inhalational anthrax, 35 days after the anthrax letter mailings of 2001, in a 94-year-old woman who was possibly exposed to contaminated mail.[64] The number of spores that must be inhaled to cause infection has been reviewed elsewhere.[65]

A report issued by the World Health Organization in 1970 estimated that if the many technical difficulties in preparation and execution were overcome, the release of 50 kg of anthrax spores would cause death or incapacity in more than 40% of the population within a 2 km radius.[66] The data that formed the basis for this estimate were not revealed.

Similarly, a Congressional Office of Technology Assessment analysis in 1993, with the same proviso, concluded that between 130 000 and 3 million fatalities would result from the release of 100 kg of *B anthracis* spores.[67] Here, too, the science on which these figures were based was not disclosed in the original source material. If these estimates are correct, multiple simultaneous attacks could devastate an army or nation.

A further factor to be considered in weighing the consequences of an anthrax attack is the issue of reaerosolization from ground and surface contamination. Anthrax spores are hardy and are believed to remain potentially infectious for decades. The risk of infection from reaerosolization of already settled spores may be exaggerated,[59,68] but the economic consequences are not. The decontamination of a single office building in Washington, DC, after the anthrax mailings of 2001 cost $23 million.[69] The decontamination of 2 postal facilities took over 2 years and cost $200 million.[70]

The Effectiveness of Antibiotics Against Anthrax

A central argument of those opposed to the vaccination program is that protection can be afforded more economically and safely through antibiotics. Animal studies have shown antibiotics to be effective in postexposure prophylaxis.[71] Postexposure vaccination alone, on the other hand, is ineffective,[2] and any additional benefit from adding vaccine to antibiotics is unproven.[2] Antibiotics are ineffective against anthrax spores, which may lay dormant for weeks in the lung before germinating; therefore, administration of antibiotics for 60 days is recommended. HHS has purchased enough antibiotics to treat 40 million Americans.[72]

Fowler et al. have produced a mathematical model, based on a 1% yearly risk of attack, arguing that combined postexposure antibiotics and vaccination would be safer and more cost-effective than mass preexposure vaccination.[73] Webb, in an accompanying editorial, notes structural problems in implementing such a plan.[70] Another mathematical model found that if mass distribution of antibiotics were completed within 6 days of exposure, at most 70% of cases could be prevented.[74] Wein et al. have also suggested considering the mass distribution of antibiotics before an attack (as well as vaccination before an attack, should one appear likely).[75]

Antibiotics were effective in dealing with the anthrax letters in 2001, but ciprofloxacin, rather than penicillin, was recommended[59] because of concern that a bioengineered agent might have been used. There are published reports that *B anthracis*

strains have been engineered to be resistant to the tetracycline class of antibiotics and the penicillins.[59] Furthermore, protective antigen has been successfully inserted into an adenovirus and vaccinia[76] and also into bacteria[77] (including *Salmonella typhimurium* and *Francisella tularensis*). The intent of these manipulations was benign, but it may be unwise to assume that future foes will lack the expertise to circumvent antibiotics.

The Stockpiling of Vaccine

Simply stockpiling vaccine is no panacea; it merely means that it will take weeks, instead of years, to immunize the public. Even if vaccines could be instantaneously administered, there is a significant time lag for immunity to develop.

For those who hold that an anthrax attack is a plausible event, the disadvantage of this plan is that it leaves the American public unprotected against a first strike. However, even if enough vaccine to immunize 300 million Americans were already stockpiled, the number who would agree to be vaccinated before an attack occurred is probably minuscule. It may take a biological event on the scale of the September 11 attacks before that attitude changes.

If a defense against an anthrax attack is to be effected, it will require the development of a vaccine that gives long-lasting protection and that the public perceives as safe and warranted. According to animal studies, the current vaccine might be effective for only 1 to 2 years after 2 inoculations.[68]

CONCLUSIONS

The medical community looks on inhalational anthrax as a disease. Our frame of reference, unfortunately, may be obsolete. It is now a weapon. Policy is no longer a matter of public health alone but also of national defense.

The determining factor here is not the lethality of *B anthracis* but the lethality of humans. Events of the past century and the technological and scientific advances of the past decades do not augur well. The notion that this weapon will not be used may be optimistic.

The essence of preparation is the making of reasonable plans for plausible worst-case scenarios. Animal studies and historical antecedent suggest that anthrax is a plausible threat. In our opinion, the prospect that private enterprise will provide a sufficient supply of anthrax vaccine is nil. Hence, government must assume responsibility for the development and production of anthrax vaccine, with the eventual intention of offering the vaccine to the public. Regardless of one's political orientation, there are some things that only government can do.[78] ■

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